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| 10/554,202 | 10/24/2005 | Robert Hugh Bradbury | 056291-5215 | 2826 |
| 9629 7590 09/12/2008 MORGAN LEWIS & BOCKIUS LLP 1111 PENNSYLVANIA AVENUE NW WASHINGTON, DC 20004 | | | | |
| EXAMINER | | | | |
| TRUONG, TAMTHOM NGO | | | | |
| ART UNIT | | PAPER NUMBER | | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/554,202

Applicant(s)

BRADBURY ET AL.

Examiner

TAMTHOM N. TRUONG

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10-24-05 (Prelim. Amdt.).
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-32 and 37-39 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-9, 16-30, 32 and 37-39 is/are rejected.
- 7) ☒ Claim(s) 10-15 and 31 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date See Continuation Sheet
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date : 1/28/08, 6/8/07, 2/27/07, 10/24/05 .

DETAILED ACTION

Applicant's preliminary amendment of 10-24-05 is acknowledged. Claims 33-36 are cancelled. Claims 1-32 and 37-39 are pending.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-9, 16-30, 32 and 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

- a. The phrase "wherein any CH,...optionally bears...one or more...(2-3C)alkanoyl..." is unclear if it means for the first carbon to be $>C=O$ because CH bearing alkanoyl would still have incomplete valence.
- b. Claim 37 recites the phrase "*converting a quinazoline derivative of the formula I into another quinazoline derivative of the formula I'*". It is unclear which derivative is converted into which.
- c. Claim 38 recites "*treating a tumour sensitive to inhibition of the erbB2*" is unclear as to which diagnostic methods or conditions that could determine the sensitivity of the tumour.

d. Claim 39 recites a "*method for selectively inhibiting erbB2 receptor tyrosine kinase*" is unclear. Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Additionally, determining whether a given disease responds or not to erbB2 receptor tyrosine kinase involves much experimentation since a negative response from one patient does not mean the drug isn't useful as no drug has 100% effectiveness. Thus what "success rate" determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? The test for determining compliance with 35 USC 112, par.two is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. **Scope of Enablement:** Claims 1-9, 16-30, 32 and 37-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making and using compounds of formula I wherein $\text{-NR}^3\text{R}^4$ is a dialkylamino, does not reasonably provide enablement for making and using the remaining compounds of formula I. The specification does

not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented;
- (3) The state of the prior art;
- (4) The relative skill of those in the art;
- (5) The predictability or unpredictability of the art;
- (6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims: The scope of R³ and R⁴ represents substituents having CH, CH₂ or CH₃ that can be further substituted with many groups such as: halogeno, hydroxyl, cyano, alkoxy, alkanoyl, alkyamino and dialkylamino. Thus the combination of substituents for R³ and R⁴ increases the number of permutations represented by formula I. Therefore, the scope is unduly broad.

The amount of direction or guidance presented: The specification provides a generic process for making compounds of formula I. However, the starting material is a (R³, R⁴)-N-(CH₂)₂-O that is already substituted with R³ or R⁴. The process does not teach how R³ and/or R⁴

can be further substituted, nor does it teach how steric hindrance of substituents on R^3 and R^4 can be prevented. Working examples are limited to compounds having $-NR^3R^4$ as a dialkylamino. Thus, the skilled chemist would not be able to extrapolate from the synthetic procedures of the disclosure to make compounds of formula I with many of the moieties instantly claimed for R^3 and R^4 . Furthermore, the established biological activity for the species made cannot be extrapolated to other compounds of formula I due to the different structural attributes of the diverse moieties claimed for R^3 and R^4 . Thus, the specification fails to provide adequate guidance for making and using the claimed compounds.

The state of the prior art: There is no reference presented on record or found in the prior art where a quinazolinone is substituted with a $-(R^3, R^4)-N-(CH_2)-O$ group that is further substituted as those claimed herein. Thus, there is no guidance in the art or provided in the instant disclosure to substantiate such diversity for making and using compounds such as those instantly claimed.

The relative skill of those in the art: Even with advanced training, the skilled artisan would have to carry out extensive research to select an effective compound from the large Markush group of compounds represented by formula I. Not only does one have to determine an IC_{50} value, but also *in-vivo* activity or some other art accepted correlative procedures to establish an LD_{50} , therapeutic indexes and pharmacokinetic profiles for the compounds of the genus. Given such a large Markush group of compounds for formula I, such a task would require a tremendous amount of effort, time and resources. The examiner establishes herein these tasks would indeed impose an undue burden upon a person attempting to practice this invention.

The predictability or unpredictability of the art & The quantity of experimentation necessary: Unpredictability in the pharmaceutical arts has been well established due to various and often conflicting biochemical pathways and complex biological factors that often affect conditions in an individual on a case by case basis . In the instant case, the specification has not provided sufficient support or guidance to shown how to make the compounds of general formula I with the extensive substitution profile asserted with complicated substitution representative of the scope asserted for the R³ and/or R⁴ moieties, much less establishing biological activity for such a broad range of generic compounds, especially as the structure diverges so much that activity recognized for the core may be and is questioned.

Thus, given the unpredictable nature of the art, the deficiencies of the disclosure and the vast array and diverse compounds claimed herein, one skilled in the art would indeed be forced to engage in undue experimentation to make and use compounds of formula I as recited in the claims as currently drafted.

3. **Scope of Enablement:** Claims 38 and 39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating breast tumour, does not reasonably provide enablement for a method of treating other tumour allegedly sensitive to inhibition of erbB2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in the determination of an enabling disclosure:

- (1) The breadth of the claims;
- (2) The amount of direction or guidance presented;
- (3) The state of the prior art;
- (4) The relative skill of those in the art;
- (5) The predictability or unpredictability of the art;
- (6) The quantity of experimentation necessary;

[See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int., 1986); also *In re Wands*, 858 F. 2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)].

The breadth of the claims:

Claim 38 recites a “method for treating a tumour sensitive to inhibition of the erbB2 receptor tyrosine kinase...”

Claim 39 recites a “method for selectively inhibiting erbB2 receptor tyrosine kinase...”

The scope of both claims covers the treatment of a myriad of cancerous and benign tumours as cited below:

kinases. Particularly, the compounds of the present invention are expected to be useful in the prevention or treatment of those tumours that are sensitive to inhibition of the erbB2 receptor tyrosine kinase that are involved in the signal transduction steps which drive proliferation and survival of these tumour cells. Accordingly the compounds of the present invention are expected to be useful in the treatment and/or prevention of a number of hyperproliferative disorders by providing an anti-proliferative effect. These disorders include, for example psoriasis, benign prostatic hyperplasia (BPH), atherosclerosis and restenosis and, in particular, erbB2 receptor tyrosine kinase driven tumours. Such benign or malignant tumours may affect any tissue and include non-solid tumours such as leukaemia, multiple myeloma or lymphoma, and also solid tumours, for example bile duct, bone, bladder, brain/CNS, breast, colorectal, cervical, endometrial, gastric, head and neck, hepatic, lung, muscle, neuronal, oesophageal, ovarian, pancreatic, pleural/peritoneal membranes, prostate, renal, skin, testicular, thyroid, uterine and vulval tumours. According to this aspect of the invention there is provided a quinazoline derivative of the formula I, or a pharmaceutically acceptable salt thereof, for use as a medicament.

The amount of direction or guidance presented: The specification provide *in-vitro* bioassays on breast tumour cell line only. It does not provide data or evidence on reduction of tumor size or cell growth for other cancers. Due to different cell morphology, the data for breast tumour cell line cannot be extrapolated to tumour of other cells such as bone, bladder, brain, gastric, etc. Thus, the specification fails to provide sufficient evidence to enable the skilled oncologist to treat all kinds of tumour encompassed by the claims.

The state of the prior art: A commercially known chemotherapeutic agent Iressa or Gefitinib which, in a preclinical studies, is shown to treat cancers such as: prostate, ovarian, breast, colon, small-cell and non-small-cell lung, and ductal carcinoma. Even for the listed cancers, "only tumors in which inhibition of the receptor results in inhibition of down stream signaling pathways are growth arrested." (see page 861 (right column), Grünwald V. et. al.,

REVIEW, J. Nat. Can. Inst., Vol. 95, No. 12, 6/18/03). Thus, the state of the art does not correlate the inhibition of EGFR (such as erbB2) to all types of cancers. Therefore, the state of the art does not support the scope of the claimed methods.

The relative skill of those in the art: There has never been a compound capable of treating cancer generally, let alone treating all kinds of tumours. Different types of cancers affect different organs and have different modes of growth and harm to the body as well as different vulnerabilities. Thus, the existence of such a “silver bullet” is contrary to our present understanding in oncology. Therefore, it is beyond the skill of oncologists today to get an agent to be effective against all cancers or all hyperproliferative disorders in general.

The predictability or unpredictability of the art & The quantity of experimentation necessary: The pharmaceutical art has been known for its unpredictability due to various conflicting path ways, or biological factors that are sometimes genetically unique to individuals. In the instant case, the data on breast tumour cells alone does not guarantee the compound’s effectiveness in treating cancers allegedly sensitive to erbB2.

See *Hoffman v. Klaus* 9 USPQ 2d 1657, and *Ex parte Powers* 220 USPQ 925 regarding type of testing needed to support *in vivo* uses.

Thus, given the unpredictable nature of the art, and the preliminary research in the art, one skilled in the art will have to carry out undue experimentation to practice the method of treatment recited in claims 38 and 39. When the best efforts have failed to achieve a goal, it is reasonable for the PTO to require evidence that such a goal has been accomplished, *In re Fereus*, 163 USPQ 609. The failure of skilled scientists to achieve a goal is substantial evidence

that achieving such a goal requires undue experimentation, *Genetech vs. Novo Nordisk*, 42 USPQ 2nd 1001, 1006.

Claim Objections

4. Claims 10-15 and 31 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The species recited in said claims do not have an “alknol” group as a substituent on R³ or R⁴.

Information Disclosure Statement

5. The IDS's of 6/8/17, 1/28/08, 2/27/07 and 10/24/05 need to have inventor names for all foreign documents. Applicant is requested to provide such information to complete the record.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TAMTHOM N. TRUONG whose telephone number is (571)272-0676. The examiner can normally be reached on M, T and Th (9:00-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system.

Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer

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Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Tamthom N. Truong/

/Deepak Rao/
Primary Examiner
Art Unit 1624
9-5-08

Tamthom N. Truong
Examiner
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